Letter to the editor:

Grating visual acuity in infantile nystagmus in the absence of image motion (response)

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Introduction

We would like to thank Dr Dell'Osso for his critique of our work, as well as for highlighting the issue of visual acuity (VA) testing in the presence of infantile nystagmus (IN). It has long been assumed that VA could be improved by reducing the intensity of the nystagmus (i.e. the average velocity of the eye movements), and as cited by Dell'Osso, there are many such claims in the literature (discussed below). Over the last few decades, this intuitively appealing view has become entrenched as the theoretical basis for numerous therapeutic interventions. Indeed, Dell'Osso's critique of our study begins and ends by appealing to this notion, but we would remind him that intuition is no substitute for scientific rigour.

Study design

In our study[1], we have demonstrated that there exists a fundamental underlying limitation in the VA of adults with IN, even in the *absence* of retinal image motion. By presenting grating stimuli using very brief flashes of light that were less than 1 ms in duration, we were able to virtually eliminate any motion blur induced by the eye movements themselves, thus unmasking the underlying VA. Subjects with IN and controls were tested under both constant and brief (tachistoscopic) lighting conditions. The brightness of the flash was adjusted so that control subjects showed no change in VA. However, contrary to the assumption that the eye movements of IN degrade VA, there was also no significant improvement whatsoever in subjects with IN when the effect of their eye movements (i.e. motion blur) was eliminated.

Clearly, Dell'Osso has missed the point of our experiment. He erroneously states that we used a flash with a duration of 75 ms, whereas the duration was, in fact, only 0.76 ms. Such

a brief presentation ensured that there was virtually *no* retinal smear caused by the nystagmus. His error is further compounded when he suggests that longer (i.e. 100 ms) presentations during foveating periods of the waveform might have worked better – a duration that long would produce substantial retinal smear and completely defeat the purpose of our experiment. Dell'Osso also expresses concern that the waveform characteristics of our participants might have affected the outcome. However, the fundamental premise of the experiment was to *circumvent* the eye movements altogether by eliminating image motion. Our paradigm thus nullified possible effect of waveform variations in order to provide a measure of the subjects' underlying spatial acuity threshold. For this reason, even if we were inclined to compute NAFX, it would have no meaning in this context. Moreover, the number of presentations available to each participant was unrestricted in order to overcome the possibility (as yet untested, despite Dell'Osso's claims) that detailed visual information cannot be gathered during non-foveating portions of the waveform. The gratings used in our study were sufficiently large that the fovea was always pointing at the stimulus whenever the flash might have occurred. Dell'Osso also argues that poorer VA for vertical rather than horizontal gratings supports the notion that VA is limited by the horizontal nystagmus, and clearly dismisses the possibility of meridional amblyopia, as originally suggested by Abadi and King-Smith[2].

Within subject measurements of VA

In our paper, we pointed out that a correlation between VA and various aspects of the nystagmus waveform (e.g. foveation duration, intensity, etc.) appears to be based on inter-subject comparisons. In rebuttal, Dell'Osso cites an impressive list of 12 papers in support of intra-subject improvement in VA[3–14], but in our view, his interpretation exaggerates any

such support. Close inspection reveals that only one of these papers actually provides statistical evidence of such a change[13] – as measured using standard letter charts. Of the other studies, six contained three or fewer subjects[4,6,7,9,11,14]. In fact, four of these studies only used one subject: Dell'Osso himself[4,7,9,14]. Two of the papers cited were reviews, and thus contained no new data[8,10], while the remaining three found statistically significant changes in nystagmus waveform characteristics, but *failed to detect significant changes in VA*[3,5,12]. In three of these studies[4,7,9], VA was not even measured, but instead NAFX was used as an outcome measure, from which VA was *predicted*. NAFX is a computed number based on waveform shape and does not include any perceptual component. Thus, these studies only confirm a change in waveform, and any claim that this reflects improvement in VA is completely circular.

Despite the lack of clear evidence in the above studies, we are aware of a handful studies that *have* found a statistically significant change in VA in response to waveform modifications. These include the work of Hertle et al.[15], who showed improvements in VA following head posture surgery, and McLean et al.[16], who treated patients with memantine and gabapentin. We did not, and would not, suggest that VA cannot be improved *at all* in every subject with IN. On the basis of our results[17,18] (and those of others[19,20]), our conclusion was, and remains, that treatments that seek to slow the eye movements of adults with IN are likely to be *fundamentally limited* with regards to the improvements that can be expected in VA.

What is VA?

Crucially, *none* of the studies that purport to have found a change in VA used strict psychophysical procedures to determine the outcome. It is worth noting that all studies of

IN that *have* involved such techniques (i.e. forced choice staircase procedure or similar) have failed to detect significant changes to VA in response to modifications of the waveform, whether through stress[17,19] or altered gaze angle[18,20]. Nonetheless, some individuals with IN report improvements in their 'vision' following treatment, as well as when viewing using their preferred gaze angle (null zone).

How might this discrepancy between VA measurement and subjective perceptual experience arise? In order to understand this, it is first worth reiterating the definition of *visual acuity*, i.e. the spatial resolution of a visual system. It has long been suspected that, due to difficulties in the accurate timing and deployment of gaze in IN, letter charts are inadequate as a sole measure of visual function. Dell'Osso himself has published at least one study that reaches this same conclusion[8].

The limitations of letter charts

Letter charts are generally assumed to provide a pure measure of the spatial resolving power of the visual system, yet there are inherent time constraints. Any good clinician will know to give their patient plenty of time before responding to a chart, and this is especially true in the case of nystagmus. Nonetheless, viewing duration is limited by the 'need to move on' to the next test, and the near absence of double-blind clinical trials in the IN literature makes it difficult to ensure that bias does not creep into the testing process when obtaining results (i.e. inadvertently allowing more time). In contrast, these issues are greatly reduced if not eliminated when using forced choice psychophysical testing. Hence, we argue that this level of discipline is necessary in order to claim that a therapeutic intervention is capable of eliciting improvements in spatial or any other visual function. Letter chart testing may ultimately turn out to be part of a sensitive test of *overall* visual function in IN.

However, it is likely that changes in VA, as measured with a letter chart, may not represent an actual change in *spatial* acuity but rather intrinsically include a *temporal* aspect of visual performance, such as target acquisition latency, that may well be influenced by changes in nystagmus intensity and/or foveation duration. As Dell'Osso himself has argued, this is why eye movement based assessments of visual function are more appropriate in patients with IN[8].

The participants in our experiment, who were comfortably seated and viewed stimuli using their null zone, did not benefit from the removal of retinal image motion. However, it remains possible that, in other studies, an unusually large *increase* in nystagmus intensity (e.g. due to stress owing to the prospect of undergoing experimental eye surgery) might result in a motion-blur-induced *worsening* of spatial acuity. Nevertheless, such a change in VA has repeatedly escaped detection in controlled psychophysical experiments. Cham et al. and Jones et al. both induced an increase in nystagmus intensity by introducing stress[17,19], but found no significant change in VA. Similarly, Erichsen et al. and Yang et al. systematically assessed VA at different gaze angles[18,20], and they too were unable to elicit statistically significant changes in VA.

The relationship between waveform and VA between subjects

The well documented correlation between VA and waveform parameters, when considering a range of *different* subjects with IN, remains to be explained. Intuitively, increasing the time the fovea spends directed towards the object of regard (i.e. increasing 'foveation' duration) might be expected improve the visual experience. Indeed, this has been demonstrated in control subjects[22]. However, in light of our results and those of others, any improvement in the vision of a given individual with IN is unlikely to involve a substantive

change in spatial acuity *per se.* We suggested in our paper that the observed inter-subject correlation may result from the waveform parameters, as measured by a metric such as NAFX, being 'matched' during development to the available VA in a given subject. This is certainly consistent with a recent longitudinal study of nystagmus in young children[23]. An important implication of this view is that, if there truly is such a thing as 'isolated' IN (i.e. IN in which there is no comorbid afferent visual system pathology), then reducing nystagmus intensity *during the critical period for visual development* might result in long-term improvements in VA.

Summary

Attempting to measure visual changes using inappropriate tools may be doing a disservice to our patients. The subjective improvements to visual function that patients sometimes report following treatment are not consistent with the disappointing improvements obtained in 'VA', which – if they occur at all – are typically less than two lines on a chart. Indeed, the ETDRS chart, a staple in vision research, is known to be relatively insensitive to such small changes, even in the absence of nystagmus[24]. Directing our efforts towards more appropriate perceptual measures than VA alone may finally provide evidence to back up anecdotal reports for the usefulness of therapies.

Dell'Osso has claimed that our conclusions might be used to "deny effective treatment to nystagmus patients". However, as we have discussed above, although the eye movements may be affected, VA has not been demonstrated to improve after changes to the waveform, which is entirely consistent with our results. Whether this reflects the inadequacy of VA as an outcome measure or the failure of such treatments to actually improve vision remains to be determined. The fact that at least some patients report "improved vision" means that we

must strive to determine what other aspects of their vision, such as “time to see”, might be affected by a given treatment. Although waveform-measuring functions such as NAFX attempt to quantify any changes in visual performance, they are unfortunately predicated on aspects of spatial visual function (VA), which have repeatedly been shown to be relatively unmodifiable, when measured appropriately.

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